

Letter to the Editor

Letter to the editor regarding “unusual extraneural metastasis of glioblastoma”

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Dear Editor,

We recently read with great interest “Unusual extraneural metastasis of glioblastoma (GBM)” by Achi *et al.*, who describe their case of a GBM lung metastasis.^[1] We appreciated their commentary on differentiating between GBM and gliosarcoma; however, we believe that their discussion was limited by a superficial overview of the mechanisms by which GBM could metastasize. We wish to provide further elaboration on the various pathways involved in GBM metastasis, with particular emphasis placed on iatrogenic and “glymphatic” mechanisms.

GBM has classically been considered incapable of extracranial metastasis since Cushing and Bailey’s famous 1926 report.^[7,9,20] However, as described by Achi *et al.*, extracranial GBM metastases have been well-reported in the literature.^[1] In fact, 0.2–2.7% of GBMs are accompanied by extracranial metastases,^[3] and up to 20% of GBM patients have circulating tumor cells present in their bloodstream.^[9] The reports describing extracranial GBM metastases in the literature are heterogeneous and reflect the various possible pathways of metastasis. Several metastatic pathways have been described, including leptomeningeal extension,^[7,9,21] cerebrospinal fluid (CSF) bulk flow,^[15] direct invasion through surrounding tissues, along cranial nerves or spinal nerves,^[11,21] hematogenous dissemination,^[5] and through the recently described “glymphatic” drainage pathway.^[20] We wish to specifically highlight the roles of iatrogenic spread and glymphatic drainage in GBM metastasis.

Iatrogenic tumor spread appears to be the main mechanism by which GBM spreads outside of the head.^[3,21] The majority of cases of extracranial GBM metastases described occurred in patients who underwent previous craniotomy, as described in Achi *et al.*’s report;^[1,13,25,26] 90–96% of extracranial GBM metastases occurred in patients who underwent prior surgery.^[19,25] Surgical intervention inadvertently aids in tumor cell spread by helping tumor cells overcome the obstacles preventing their metastasis, such as the blood–brain barrier (BBB), poor fibronectin expression by tumor cells, and the dense encasement afforded by the dura.^[9,18] In addition to surgery, radiation therapy has also been described to promote tumor dissemination by promoting vascular invasion.^[9,18,21] Adjunctive procedures commonly performed in GBM patients have also been reported to cause extracranial GBM metastases, including brain biopsy and ventriculoperitoneal shunting.^[10]

However, it is important to note that cases of extracranial GBM metastases have been reported independent of any intervention,^[2,9,18] and it is possible for tumor cells to overcome the barriers

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to their spread unaided.^[19] We agree with Sun *et al.*, who state that great care should be taken by the operating surgeon to minimize the risk of tumor cell spread.^[21] Several actions can be taken to minimize this risk, including adhering to the principles of a nontumor operation, changing gloves and instruments after tumor resection, thoroughly rinsing the surgical field with saline and chemotherapeutics, ensuring an intact dura during closure, and utilizing appropriate adjunctive therapies during the perioperative period.^[21,24,25] Most extracranial GBM metastases follow craniotomy, as evidenced by Achi *et al.*'s case, and surgery is the major mechanism responsible for facilitating tumor spread.^[1]

The brain does not contain a traditional lymphatic drainage system; however, a recently described “glymphatic” system has revolutionized the understanding of intracranial fluid dynamics.^[4,12] Briefly, the periaxonal spaces surrounding penetrating arteries and arterioles (Virchow-Robins space) contain CSF, which is subsequently transported across the BBB by aquaporin-4 channels on astrocyte end feet. The transported CSF mixes with the interstitial fluid of the brain parenchyma and is subsequently transported out across the BBB into the perivenous spaces surrounding the deep cerebral veins. These perivenous spaces drain into the dural lymphatics, which ultimately exit the skull and drain into the deep cervical lymph nodes and the systemic circulation.^[4,12,19,20] It has been postulated that GBM metastases may occur through this drainage system, as GBM metastases appear to have a predilection for the deep cervical lymph nodes; in fact, 51% of reported extracranial GBM metastases occur in the cervical lymph nodes.^[17,26] Furthermore, there have also been several reports of GBM metastases to the parotid gland, which is imbued with a rich lymphatic network during embryological development.^[3,14,22,23] Similar to hematogenous dissemination, dural defects created during surgery facilitate tumor cell invasion into the dural lymphatics, and the majority of lymph node metastases occur after prior craniotomy.^[2] Nevertheless, we believe the hypothesis that this newly described glymphatic network can independently facilitate that metastasis is valid, as cases of cervical lymph node metastasis have been described independent of surgical intervention.^[5,6,8] Current research into the glymphatic system is focused mainly on Alzheimer's disease, stroke, and traumatic brain injury,^[12] but we believe that there are important implications for neuro-oncology.

The low reported rate of GBM metastasis is due to the rate of mortality before the development of a recognizable extracranial tumor:^[16] The median time between GBM diagnosis and verified GBM metastasis is 2 years,^[26] while the median survival of GBM following initial diagnosis is 13 months.^[9] We hypothesize that extracranial GBM metastases may begin to present clinically significant problems as GBM survival increases;^[18,20,21,22,25] furthermore, extracranial GBM management protocols do not currently

exist.^[5,9,21,22,25] Until protocols are developed, we recommend attempting to limit the impact of iatrogenic tumor spread during surgery.^[21,24,25] Research into the glymphatic system is ongoing, and we are interested to learn about the potential implications that it may have on neuro-oncology and extracranial metastasis. In conclusion, we commend Achi *et al.*^[1] for a fine description of their unusual case of extracranial GBM metastasis, and we hope to supplement their discussion with a brief description of iatrogenic and glymphatic tumor spread.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The author(s) confirms that there was no use of Artificial Intelligence (AI)-Assisted Technology for assisting in the writing or editing of the manuscript and no images were manipulated using the AI.

REFERENCES

1. Achi J, Achi XW, Veintimilla P, Cueva J. Unusual extraneural metastasis of glioblastoma. *Surg Neurol Int* 2023;14:218.
2. Alhoulaiby S, Abdulrahman A, Alouni G, Mahfoud M, Shihabi Z. Extra-CNS metastasis of glioblastoma multiforme to cervical lymph nodes and parotid gland: A case report. *Clin Case Rep* 2020;8:1672-7.
3. Baskurt O, Kurtulus Y, Yavuz AY, Avci İ. Extracranial metastasis of recurrent glioblastoma to the parotid gland: A case report and review of the literature. *Egypt J Neurosurg* 2022;37:25.
4. Benveniste H, Liu X, Koundal S, Sanggaard S, Lee H, Wardlaw J. The glymphatic system and waste clearance with brain aging: A review. *Gerontology* 2019;65:106-19.
5. Carvalho J, Barbosa CC, Feher O, Maldaun MV, Camargo VP, Moraes FY, *et al.* Systemic dissemination of glioblastoma: Literature review. *Rev Assoc Med Bras* (1992) 2019;65:460-8.
6. Chretien F, Gray F, Funalot B, Authier FJ, Peltier E, Lange F, *et al.* Extracerebral metastases of a glioblastoma, in the absence of surgery. *Arch Anat Cytol Pathol* 1995;43:342-9.
7. Cushing H, Bailey P. A classification of the tumors of the glioma group on a histogenetic basis with a correlated study of prognosis. *J Am Med Assoc* 1926;87:268.
8. Dolman CL. Lymph node metastasis as first manifestation of

- glioblastoma. Case report. *J Neurosurg* 1974;41:607-9.
9. Ghous G, Miller D, Doll D, Tuncer T. A rare case of glioblastoma with extensive liver metastases. *Oncology (Williston Park)* 2021;35:733-40.
10. Granados AM, Zuniga N, Ospina C, Merchancano L. Secondary glioblastoma with abdominal metastasis: Case report. *Radiol Case Rep* 2018;13:347-51.
11. Hamilton JD, Rapp M, Schneiderhan T, Sabel M, Hayman A, Scherer A, *et al.* Glioblastoma multiforme metastasis outside the CNS: Three case reports and possible mechanisms of escape. *J Clin Oncol* 2014;32:e80-4.
12. Jessen NA, Munk AS, Lundgaard I, Nedergaard M. The glymphatic system: A Beginner's guide. *Neurochem Res* 2015;40:2583-99.
13. Liu J, Shen L, Tang G, Tang S, Kuang W, Li H, *et al.* Multiple extracranial metastases from glioblastoma multiforme: A case report and literature review. *J Int Med Res* 2020;48. Doi: 10.1177/0300060520930459
14. Ogungbo BI, Perry RH, Bozzino J, Mahadeva D. Report of GBM metastasis to the parotid gland. *J Neurooncol* 2005;74:337-8.
15. Onda K, Tanaka R, Takahashi H, Takeda N, Ikuta F. Cerebral glioblastoma with cerebrospinal fluid dissemination: A clinicopathological study of 14 cases examined by complete autopsy. *Neurosurgery* 1989;25:533-40.
16. Pasquier B, Pasquier D, N'Golet A, Panh MH, Couderc P. Extraneural metastases of astrocytomas and glioblastomas: Clinicopathological study of two cases and review of literature. *Cancer* 1980;45:112-25.
17. Piccirilli M, Brunetto GM, Rocchi G, Giangaspero F, Salvati M. Extra central nervous system metastases from cerebral glioblastoma multiforme in elderly patients. Clinicopathological remarks on our series of seven cases and critical review of the literature. *Tumori* 2008;94:40-51.
18. Rosen J, Blau T, Grau SJ, Barbe MT, Fink GR, Galldiks N. Extracranial metastases of a cerebral glioblastoma: A case report and review of the literature. *Case Rep Oncol* 2018;11:591-600.
19. Rossi J, Giaccherini L, Cavallieri F, Napoli M, Moratti C, Froio E, *et al.* Extracranial metastases in secondary glioblastoma multiforme: A case report. *BMC Neurol* 2020;20:382.
20. Stoyanov GS, Petkova L, Iliev B, Ali M, Toncheva B, Georgiev R, *et al.* Extracranial glioblastoma metastasis: A neuropathological case report. *Cureus* 2023;15:e35803.
21. Sun Q, Xu R, Xu H, Wang G, Shen X, Jiang H. Extracranial metastases of high-grade glioma: The clinical characteristics and mechanism. *World J Surg Oncol* 2017;15:181.
22. Swinnen J, Gelin G, Fransis S, Vandevenne J, Van Cauter S. Glioblastoma with extracranial parotid, lymph node, and pulmonary metastases: A case report. *Radiol Case Rep* 2019;14:1334-47.
23. Taha M, Ahmad A, Wharton S, Jellinek D. Extra-cranial metastasis of glioblastoma multiforme presenting as acute parotitis. *Br J Neurosurg* 2005;19:348-51.
24. Undabeitia J, Castle M, Arrazola M, Pendleton C, Ruiz I, Urculo E. Multiple extraneural metastasis of glioblastoma multiforme. *An Sist Sanit Navar* 2015;38:157-61.
25. Wu X, Wang J, Wang Y. Multiple intracranial and extracranial metastases from postoperative glioblastoma: A case report and review of the literature. *Interdiscip Neurosurg* 2021;24:101025.
26. Zhang W, Cai YY, Wang XL, Wang XX, Li Y, Han GY, *et al.* Bone metastases of glioblastoma: A case report and review of the literature. *Front Oncol* 2021;11:705455.

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